(12) UK Patent Application (19) GB (11) 2 327 344 (13) A

(43) Date of A Publication 27.01.1999

(21) Application No 9715079.1

(22) Date of Filing 18.07.1997

(71) Applicant(s)
Ninh Thuy On
36 Spray Street, Woolwich, LONDON, SE18 6AG,
United Kingdom

(72) Inventor(s)
Ninh Thuy On

(74) Agent and/or Address for Service
Ninh Thuy On
36 Spray Street, Woolwich, LONDON, SE18 6AG,
United Kingdom

(51) INT CL[6]
A61K 31/415

(52) UK CL (Edition Q)
A5B BJA B273 B281 B466 B480 B503 B513 B523 B542 B565 B586 B641 B644 B650 B656 B661 B664 B826 U1S S2410

(56) Documents Cited
US 5571521 A

(58) Field of Search
UK CL (Edition P) A5B BJA
INT CL[6] A61K 31/415
ONLINE:CAS-ONLINE, WPI

(54) Abstract Title

Pharmaceutical compositions containing phenytoin and either an azole anti-fungal/anti-bacterial agent and/or a silver salt for topical application

(57) A pharmaceutical composition comprising a phenytoin type compound and either an azole anti-fungal/anti-bacterial agent and/or a silver salt compound. The composition may also comprise hydrogel, hydrophilic or hydrophobic ointments containing phenytoin. These compositions are applied topically and are useful in the treatment of wounds, ulcers, burns, pressure sores or skin lesions that are at risk of infection.

GB 2 327 344 A

PHARMACEUTICAL COMPOSITIONS CONTAINING PHENYTOIN, ANTI-BACTERIAL AND/OR ANTI-FUNGAL AGENTS FOR TOPICAL APPLICATION

BACKGROUND

Diphenyl hydrantoin or phenytoin [5,5-diphenyl-2,4 imidazolidinedione] is an anti-convulsant. Phenytoin, its derivatives, and compositions containing the same are well known in the art, see US Pat. nos 2409754; 3932449; 3798233; 4093809, the disclosure which are incorporated herein.

Many uses of phenytoin and its derivatives have already been disclosed including its role of phenytoin in wound healing. While the experimental data supporting the use of phenytoin in wound healing suffered flaws in their experimental design, the evidence is overwhelming [Anstead G M *et al*, The Annals of Pharmacotherapy, 1996, Vol 30: 768-774]. These studies were conducted using phenytoin from the contents of Dilantin or Epanutin capsule.

To date, applicant knows that the use of topical phenytoin for wound management is limited due to lack of a suitably presentable formulation. Applicant also believes that if a wound healing promoter and anti-infective agents are available as one preparation, one would find such an administration form more convenient and useful for those wounds susceptible to infections.

US 5571521A disclosed the compositions containing silver ammonium phenytoin complex and a phenytoin and use of said composition. Two component preparations of silver sulphadiazine and a benzocaine anaesthetic, silver sulphadiazine and azole anti-fungal/anti-bacterial agent are described in WO9204029 and US4803066, respectively.

As far as the inventor knows, the art has never suggested that a phenytoin to be added to azole anti-fungal/anti-bacterial agents, selected silver ions or both of these groups of compounds. Also, the prior art does not suggest the use of any two-component compositions of a phenytoin and an azole anti-fungal/anti-bacterial, a phenytoin and a selected silver ion compound; and three component compositions of a phenytoin, an azole anti-fungal/anti-bacterial agent and a selected silver ion compound to manage wounds, ulcers, burns or other skin lesions exposed to the risks of infection.

Accordingly, one aspect of this invention is to provide a formulation for delivering phenytoin topically. Another aspect of this invention is provide convenient useful compositions for managing wounds that are at risks of infection.

SUMMARY

The present invention relates to pharmaceutical compositions consisting of a phenytoin, an azole anti-fungal/anti-bacterial agent, or/and a silver ion compound. Specifically, it relates to hydrogel, hydrophilic and hydrophobic compositions comprising phenytoin alone, or phenytoin plus an anti-bacterial/ an anti-fungal agent, or phenytoin plus an anti-fungal/anti-bacterial together with a silver ion compound. These preparations are useful in the treatment of wounds, ulcers, burns, pressure sore or skin lesions at risks of infection.

DETAILED DESCRIPTION

A phenytoin compound for use in the present invention includes, but not limited to, phenytoin as a free form, sodium phenytoin. Structurally related phenytoin derivatives having similar enhancement of wound healing properties are also intended to be encompassed by this group. Suitably, the amount of phenytoin which will be present in the present invention will be from 0.1 - 10% by weight, for example 2%.

The azoles for use in the compositions and methods of the present invention can be selected from the following categories:

1. Clotrimazole and its derivatives

2. Miconazole and its derivatives

3. Econazole and its derivatives

4. Metronidazole and its derivatives

The silver ion compound present in the compositions of the invention may be any of those which is suitable for topical application in, for example, the treatment of burns, including silver salts such as silver nitrate, silver sulphate, silver phosphanilide and the like, silver sulphonamides such as silver sulphadiazine. More suitable silver compounds are silver sulphonamides and preferred is silver sulphadiazine.

The amounts of the medicament(s) in the composition of the present invention vary depending upon the particular medicament(s) employed but in all instances will be an mount effective for its/their intended purpose. Suitably, the amount of an azole compound which will be present in the compositions of the present invention will be from 0.1% to 10% by weight of the azole compound. For examples, clotrimazole, miconazole, econazole and metronidzole can used at 1%, 2%, 1% and 0.75% by weight, respectively. These azoles are sometimes administered in the form of their pharmaceutically acceptable salts, e.g nitrate salts. Suitably, the amount of silver compound which will be present in the compositions of the present invention will be from 0.1 to 10% by weight of the silver compound. For example, silver sulphadiazine can be used at 1% by weight.

The pharmaceutical compositions of the present invention would be suitable for topical treatments of ulcers, wounds, burns, pressure sores, as well as other skin lesions exposed to the risk of infection.

Suitable forms of the topical compositions of the present invention include gels, ointments, creams, sprays, suspensions, solid forms such as powder and the like, emulsions, lotions and films. The mixture can also be incorporated into medicated dressings and into adhesives used on polymeric film dressings such as Opsite.

A topically administrable composition of the invention will preferably be in the form of a hydrogel. Polymers for use in the compositions of the present invention include, but not limited to, the following hydrogels: cellulose derivatives such as carboxymethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, natural gums and the like, copolymers of polyethylene-polyoxypropylene diol block, polyacrylic acids, poly(ethylene oxide), poly(ethylene glycol), poly(vinyl alcohol), poly(vinyl pyrrolidine), poly(acrylic acid), poly(hydroxy ethyl methacrylate), and chitosan and mixtures thereof. The amount of the gelling agent present in the compositions is from 0.05 to 20% by weight. The compositions preferably comprise from about 0.02% to 10% w/v of a dispersant, preferably sodium carboxymethyl cellulose and preferably one or more pharmaceutical actives. It is appreciated that care must be taken to avoid using gelling agents which are incompatible with the silver ions and phenytoin.

In a second aspect, the compositions of the present invention will be in the form of a hydrophobic ointment. Suitable hydrophobic ointments are those formed from white or yellow soft paraffin and an oil such as liquid paraffin, castor oil, arachis oil, almond oil, olive oil, wheatgerm oil, corn oil, safflower oil, ground nut oil, sunflower oil, grapeseed oil, mineral oil in a proportion of 9:1 to 1:1. Hydrophobic ointments may also include non-ionic surfactants which may aid the miscibility of the ointment with the wound fluid and the release of medicament(s).

In a further aspect, the composition of the invention may be prepared by merely incorporating or homogeneously admixing finely divided active ingredients with the hydrophilic carrier or base. A particularly suitable hydrophilic phase is an oil-in-water emulsion consisting of 0-25% of petrolatum or liquid paraffin, 2-40% fatty C_{16}-C_{22} alcohol, 0-16% of an emulsifying agent (preferably non-ionic), 0-15% emollient, 5-40% polyhydric alcohol as a humectant and the balance to 100% being deionised or distilled water. Suitable fatty alcohols are those conventionally used and are water insoluble including, but not limited to, stearyl alcohol, cetyl alcohol, lauryl alcohol and myristyl alcohol. A suitable humectant would be propylene glycol, sorbitol, or glycerin or mixture thereof, all being water soluble compounds. Suitably, as an emulsifying agent, glyceryl fatty acid esters and the like such as sorbitan monooleate or glyceryl momostearate, are satisfactory. An emulsifying wax may also be used in place of both or part of both of the fatty alcohol and non-ionic surfactant.

Generally, where a salt of phenytoin such as sodium phenytoin is being used, the pH of the composition is preferably in the region > 9 to avoid precipitation of phenytoin free base from sodium phenytoin. Also, in order to minimise precipitation caused by absorption of atmospheric carbon dioxide, the preparations should be packaged in an air tight container.

The following examples illustrate embodiments of the subject invention wherein both essential and optional ingredients are combined.

Example 1: Hydrogel composition containing phenytoin as active.

Ingredient	Weight %
Sodium carboxymethyl cellulose	5
Propylene Glycol	40
Phenytoin sodium salt	2
Triethanolamine	1.0
Diethylamine	0.12
Distilled water to	100

(i) Add approx. 80% of the quantity of water and propylene glycol to a suitable container equipped with a high shear mixer and sweeps.

(ii) Add sodium phenytoin slowly and mix until homogenous.

(iii) Add triethanolamine and diethylamine to the batch and mix until homogenous.

(iii) Add carboxymethyl cellulose to the batch and mix until homogenous.

(iv) Balance the formula with distilled water.

(v) Pass the batch through a homogeniser at 1000-1200 psig

(vi) Package in plastic squeeze bottles/tubes.

Example 2: Hydrophobic ointment containing phenytoin as active

Ingredient	Weight %
Phenytoin free base	2
Castor oil : WSP (2:8) to	100

(i) Melt white soft paraffin and castor oil together then thoroughly mix them

(ii) Add phenytoin free base and stir until homogenous.

(iii) Allow to cool then pack.

Example 3: A cream formulation containing phenytoin as active ingredient

Ingredient	Weight %
Cetomacrogol emulsifying wax	15
Propylene Glycol	25
Phenytoin sodium salt	2
Triethanolamine	0.6
Liquid paraffin	10
White soft paraffin	12
Distilled water to	100

(i) Melt the cetomacrogol emulsifying wax and liquid paffarin together.

(ii) Dissolve the phenytoin in propylene glycol and water, add triethanolamine and stir well until homogenous.

(iii) Warm the phenytoin mixture to about the same temperature as the molten cetomacrogol emulsifying wax/liquid paraffin.

(iv) Mix the two mixtures together, adjust to weight then stir well until cool.

Example 4: Hydrogel composition containing phenytoin and silver sulphadiazine as actives

A two component hydrogel formulation is prepared in a similar manner to that described in Example 1 except that the formulation contains phenytoin sodium salt 2% and silver sulphadiazine 1% as active ingredients.

Example 5: A hydrophobic ointment containing phenytoin and silver sulphadiazine as actives

Ingredient	Weight %
Phenytoin free base	2
silver sulphadiazine	1
Liquid paraffin : WSP (3:7) to	100

(i) Melt the liquid paraffin and white soft paraffin together then thoroughly mix them

(ii) Add phenytoin free base and silver sulphadiazine then stir until homogenous.

(iii) Allow to cool then pack.

Example 6: A cream containing phenytoin and clotrimazole as active ingredients

A two-component hydrophilic ointment is prepared in a similar manner to that described in Example 3 except that the formulation contains phenytoin sodium salt 2% and clotrimazole 1% as active ingredients.

Example 7: Hydrophobic ointment containing phenytoin and clotrimazole as active ingredients

A two component hydrophobic ointment is prepared in a similar manner to that described in Example 5 except that the formulation contains phenytoin sodium salt 2% and clotrimazole 1% as active ingredients.

Example 8: Hydrogel composition containing phenytoin, silver sulphadiazine and miconzole

A three-component hydrogel formulation is prepared in a similar manner to that described in Example 1 except that the formulation contains phenytoin sodium salt 2%, silver sulphadiazine 1% and miconazole nitrate 2% as active ingredients.

Example 9: Hydrophobic ointment containing phenytoin, silver sulphadiazine and metronidazole

A three component hydrophobic ointment is prepared in a similar manner to that described in Example 5 except that the formulation contains phenytoin sodium salt 2%, silver sulphadiazine 1% and metronidazole 1% as active ingredients.

Example 10: A cream containing phenytoin, clotrimazole and silver sulphadiazine

A three component hydrophobic ointment is prepared in a similar manner to that described in Example 3 except that the formulation contains phenytoin sodium salt 2%, clotrimazole 1% and silver slphadiazine 1% as active ingredients.

As it will be apparent to those skills in the art, many modifications and alterations are possible, in the light of the foregoing disclosures, without departing from the spirits of this invention.

CLAIMS

1. A pharmaceutical composition in topical formulation comprising:

(i) a phenytoin compound in free form or pharmaceutically acceptable salt form, and

(ii) either an azole anti-fungal/anti-bacterial derivative or pharmaceutically acceptable salt thereof selected from clotrimazole, miconazole, econazole and metronidazole,

(iii) or/and a silver salt selected from silver nitrate, silver sulphate, silver phosphanilide and silver sulphonamide.

2. A topical hydrogel composition consisting essentially of:

(i) from about 0.01% to 10% phenytoin in free form or pharmaceutically acceptable salt form as an active ingredient

(ii) from about 0.02% to 20% of water soluble polymer selected from the group consisting of cellulose derivatives, co-polymers of polyethylene polyoxypropylene diol, polyacrylics, natural gums and the like, poly vinyl alcohol, poly vinyl pyrrolidine, chitosan and mixtures thereof.

3. A hydrophobic ointment consisting essentially of:

(i) from about 0.01% to 10% phenytoin in free form or pharmaceutically acceptable salt form as an active ingredient

(ii) a hydrophobic ointment base made up of about 1 to 50% of a liquid oil selected from castor oil, liquid paraffin, arachis oil, almond oil, olive oil, wheatgerm oil, corn oil, safflower oil, ground nut oil, grapeseed oil, sunflower oil; mineral oil and white/yellow soft paraffin.

4. A hydrophilic ointment (cream) consisting essentially of:

(i) from about 0.01% to 10% phenytoin in free form or pharmaceutically acceptable salt form as an active ingredient

(ii) a hydrophilic ointment base.

5. A method for treating wound or tissue for healing which comprises the administration thereto of a composition, in a topically acceptable carrier, in accordance to claim 1.

6. A composition according to claim 1, said composition being formulated as a hydrogel.

7. A composition according to claim 1, said composition being formulated as an ointment.

8. A composition according to claim 1, said composition being formulated as a cream

9. A composition according to claim 1, said composition being formulated as a spray powder.

10. A composition according to claim 1, said composition being formulated as a powder.

11. A composition according to claim 1, said composition being formulated as a lotion.

12. A composition according to claim 1, said composition being formulated as a foam.

13. A composition according to claim 1, said composition being formulated as a lotion.

14. A composition according to claim 1, said composition and a fibrous carrier.

15. A composition according to claim 14, wherein said fibrous carrier is a bandage wherein said active components are coated in impregnated into or dispersed within said carrier.

The Patent Office

7

Application No:	GB 9715079.1	**Examiner:**	William Thomson
Claims searched:	1 and 5-15	**Date of search:**	8 October 1998

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.P): A5B (BJA)

Int Cl (Ed.6): A61K 31/415

Other: ONLINE:CAS-ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
A	US 5571521A (LASKER)	

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.